REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the claims

Claims 8 and 14 were previously cancelled without disclaimer or prejudice thereof.

Claim 1 is currently being amended to recite a bio-molecule-containing fluid having a temperature of "at least 50°C" instead of "at least about 40°C". Exemplary support for the amendment is found throughout the specification, for example at page 4, lines 8, 11 and 20 and page 9, line 4. Claim 1 has also been amended to recite "water from the food and/or feed industry" instead of "process water from the food and/or feed industry" as suggested by the examiner. Exemplary support is found throughout the specification, for example at page 7, lines 7-9. As the amendments adds no new matter, entry and examination thereof is respectfully requested.

After amending the claims as set forth above, claims 1-7, 9-13 and 15-17 are pending and under examination in this application.

II. Claim interpretation

As explained in detail below, the examiner has misinterpreted the phrase "linear flow rate" in the claims. That misunderstanding has the effect of negating, in patentability terms, one of the novel and surprising aspects of applicant's claimed methodology. Conversely, a correct reading of this phrase underscores the *very high linear flow rates* that the claims prescribe and that unambiguously distinguish the claimed methodology over the methods of the cited art.

The examiner interprets "linear flow rate of at least 1,500 cm/hour" to encompass a range of flow rates, depending on column size. Thus, the examiner asserts that "any flow rate represented by cm/hour or cm/min are obvious and/or anticipates each other unless column diameter is limited to a specific size…." (Office Action at page 2). Applicants must disagree, however, and wish to clear up

an apparent misunderstanding between "linear flow rate" and "volumetric flow rate," which are distinct notions in the art.

In the field of chromatography, it is important to standardize flow rates for columns of different dimensions. This is done by expressing the flow rate as linear flow rate (cm/h, or similar units). The *linear flow rate* is defined as the *volumetric flow rate* (cm^3/h) per unit cross-sectional area (cm^2) of a given column. The diameter of the column (which of course is variable) is then removed from consideration.

Defining the flow rate independently of the column dimensions is important, because it means that the retention time (the length of time a substance takes to elute from the column) is the same, regardless of the column. A method described in terms of "linear flow rate" can be reproduced on any diameter of column, and will provide reproducible retention times.

"Linear flow rate" is the only reliable parameter for use in the field of chromatography; only methods which are described in terms of linear flow rate can be successfully transferred from one column to another.

As the cited documents evidence, linear flow rate is a well-established parameter in the field of chromatography. For example, see WO 02/096215, page 13, lines 23 and 33 (claims 2 and 3), PHARMACIA HANDBOOK (1997), p. 6 in the last paragraph, US 5,837,826 (Flickinger *et al.*), especially Table V, and Lihme *et al.*, *Meth. Biotechnol.*, 2000, p.134 at Table 5. Comparing the presently recited flow rates with those of the cited references should be straightforward, moreover, since "linear flow rate" appears in the present application and the cited art alike.

On the other hand, when the examiner has asserted that *"...any flow rate represented by cm/hr or cm/min are obvious and/or anticipates each other unless column diameter is limited to a specific size...,"* he has not pointed out the column diameter in any particular reference; nor did he present any calculations that might support this position. Accordingly, the examiner's position must be seen to derive from speculation or a misunderstanding of the phrase "linear flow rate."

For instance, the examiner cites page 45 of WO 02/096215 (Lihme), in which three columns of diameter 1.5m can extract a 690,000 L whey stream per day (= 28,750L/hour). See point 7 of the Office Action at page 5. As demonstrated below, however, only a *low* linear flow rate is obtained when one carries out the calculation in reverse, to determine linear flow rate, based on the specific values for volume flow and column diameter in the example:

First, calculate the cross-sectional **area** of a column with diameter 1.5m:

$$A = \pi r^2$$

$$\pi r^2 = \pi(0.75)^2 = 1.766 m^2$$

Next, calculate the **linear flow rate**. As noted above, the linear flow rate is the **volumetric flow rate** (m^3/hour) divided by **cross sectional area** of the column (m^2).

$$(m^3/hour) / m^2 = m/hr$$

The **volumetric flow rate** of the three columns in Example 19 is 28750L/h = $28.750\ m^3/hour$.

$$Linear\ flow\ rate: (28.750\ m^3/hr) / (1.766 m^2) = 16.28 m/hr$$

However, this is the total flow rate for **three** columns. Accordingly, this flow rate must be **divided by three** to establish the flow rate **per column.**

$$(16.28\ m/hr)/3 = 5.426\ m/hr\ which\ is\ 542.6\ cm/hr.$$

This is significantly less than "at least 1,500 cm/hour," as presently recited.

The preceding page of Lihme (page 44) describes the same volumetric flow rate for a two-column system, in which each column has a diameter of 1.5 meters. In this situation, the linear flow rate calculation would be identical to the calculations above, except the last step would include dividing by 2 (two columns) instead of 3:

$$(16.28\ m/hr)/2 = 8.14\ m/hr\ which\ is\ 814\ cm/hr.$$

Again, this value is significantly less than the "at least 1,500 cm/hr" claimed.

Further, the examiner relies on claims 15 and 17 to support his interpretation, stating that the flow rate of claim 1 must be broader *[than these claims]* to encompass the flow rate of claims 15 and 17. Office Action at page 2.

This assertion is based on a misunderstanding of claims 15 and 17, however. These claims do not recite a flow rate *per se*, rather they recite the volume of fluid applied *per litre of absorbent* per hour. Accordingly, the claims relate to a completely different operating parameter than that of claim 1, as claims 15 and 17 require the volume of absorbent to be known. The examiner mistakenly interpreted the volumes provided in claims 15 and 17 as *"volumes per hour"*, however, such an interpretation would require that the feature *"per litre of absorbent"* be ignored. Such a claim interpretation is clearly erroneous in light of the definition of linear flow rate and the language of claims 15 and 17.

Applicants submit, therefore, that "linear flow rate" means **volumetric flow rate** (*e.g.*, cm^3/hour or m^3/hour) divided by **cross sectional area** of the column (cm^2 or m^2), and that the linear flow rate value therefore is independent of column size (*e.g.*, cross-sectional area of the column). This definition comports not only with applicants' specification and claims but also with common usage of a well-known chromatographic parameter, a standard in the art.

III. Priority

The examiner asserts that the recitation of "at least 40°C" is not supported by the priority document, whereby the present claims benefit from a priority date of March 19, 2004 (Office Action at page 3). Solely to expedite prosecution, without conceding to the examiner's assertion, applicants have revised the claims to recite "at least 50°C." See support in the priority document, *e.g.*, at page 2, lines 27 and 31, at page 4, lines 18 and 21, and at page 8, lines 13 and 16-17. Thus, the pending claims have an effective date of March 21/2003, the filing date of Denmark PA 00443.

IV. Claim objections

Claims 1-7, 9-13, and 15-17 are subject to objection because the examiner feels that "process water from the food and/or feed industry" in claim 1 should be changed to "processed water" or

"water from the food and/or feed industry," thereby to "improve the format" of the claim. (Office Action at page 4).

Without conceding to the correctness of the examiner's assertion and solely to expedite prosecution, claim 1 has been amended to recite "water from the food and/or feed industry." Accordingly, the objection is obviated and should be withdrawn.

V. Claim rejection – 35 U.S.C. § 102(b)

Claims 1-7, 9-13 and 15-17 are rejected for alleged anticipation by WO 02/096215 to Lihme et al. In addition, claims 1, 3-7 and 9-13 likewise are rejected over U.S. Patent No. 5,837,826 to Flickinger et al. Applicants respectfully traverse each of these grounds for rejection, as neither Lihme nor Flickinger discloses each and every element of the claims, either expressly or inherently, in as complete detail as is contained in the claims. *See, e.g.*, MPEP §2321, citations omitted. The surprising element of the present invention is that a high productivity can be realized at *very high flow rates* when the *temperature is elevated* to levels where microbial growth is inhibited. Neither Lihme nor Flickinger provides a method which includes a high linear flow rate in conjunction with high temperature.

A. Lihme

Lihme discloses methods and compositions related to fractionation of protein-containing mixtures such as milk and milk products, vegetable and fruit derived products, and fish and fish derived products. (Lihme at abstract). Lihme also discloses the use of Expanded Bed Adsorption ("EBA") as a chromatographic separation technique (*see e.g.*, Lihme at page 2, lines 35-38; page 7, lines 38-39), the use of adsorbents which "despite having a small particle diameter and a very high density, exhibit a high binding capacity for the desired protein" (Lihme at page 7, lines 33-36), and "an EBA process … at linear flow rates above at least 200 cm/hour" (*id.* at page 8, lines 2-4).

Lihme discloses a variety of prophetic linear flow rate ranges for the disclosed chromatographic methods, from a low of 3 cm/min (180 cm/hr) to a high of 25-50 cm/min (1,500-3000 cm/hr). For instance, see Lihme at page 13, lines 22-35. The middle column of Table 1 below

summarizes the flow rates presented in Lihme, both prophetic and as described in the Experimental Examples.

With respect to temperature, Lihme is nearly silent. A single experiment in Example 11 illustrates the effects of loading temperature for fractionation of lactoperoxidase and lactoferrin from sweet whey. As shown in Table 1, column 3, the loading temperatures tested in Example 11 were 4°C, 22°C and 50°C, while the linear flow rate for this experiment was 450 cm/hr.

As Lihme does not provide information regarding temperature for sample loading or for fractionation, we must look to conventions in the art to determine what temperature Lihme most likely used. With specific reference to Lihme, the present specification states that "[c]onventionally, these methodologies have been carried out using temperatures *in the range of about 10°C*." (Specification at page 1, lines 31-35, emphasis added). Accordingly, it is presumed that the majority of the fractionations described in Lihme were carried out under conventional conditions, and that the temperature of the samples was "in the range of about 10°C." A summary of the temperatures actually disclosed in Lihme in Example 11 is provided in column 3 of Table 1. For the remaining Examples and prophetic linear flow rate ranges for which no temperature information was provided, the "conventional temperature" is presumed (see col. 3 of Table 1).

Table 1: linear flow rates and temperatures in Lihme fractionation methods

Reference	Linear flow rate	temperature
prophetic range Page 13, lines 22-39	**1500 - 3000 cm/min** (prophetic range)	in the range of about 10°C
Example 7 Page 30, line 13	7.5 cm/min (450 cm/hr)	in the range of about 10°C
Example 8 Page 33, line 10	7.5 cm/min (450 cm/hr)	in the range of about 10°C
Example 9 Page 34, line 14	7.5 cm/min (450 cm/hr) 10 cm/min (600 cm/hr) 15 cm/min (900 cm/hr) **25 cm/min (1,500 cm/hr)**	in the range of about 10°C
Example 10 Page 35, line 14	7.5 cm/min (450 cm/hr)	in the range of about 10°C
Example 11 Page 36, line 16	7.5 cm/min (450 cm/hr)	4°C 22°C **50°C**
Example 12 Page 38, line 9	10 cm/min (600 cm/hr)	in the range of about 10°C
Example 13 Page 39, line 13	300 cm/hr	in the range of about 10°C
Example 14 Page 40, line 2	450 cm/hr	in the range of about 10°C
Example 15 Page 40, line 33	450 cm/hr	in the range of about 10°C
Example 16 Page 41, line 20	450 cm/hr	in the range of about 10°C
Example 17 Page 42, lines 11-14	300 cm/hr 450 cm/hr 600 cm/hr	in the range of about 10°C
Example 18 Page 43, line 26 Page 44, line 9	900 cm/hr 450 cm/hr	in the range of about 10°C
Example 19 Page 44, lines 26-28 Page 45, lines 1-2	542.6 cm/hr 814 cm/hr	in the range of about 10°C
Example 22 Page 47, line 23	25 cm/min (1,500 cm/hr)	in the range of about 10°C

A brief review of Table 1 reveals that none of the fractionation experiments were performed at a high temperature (at least 50°C) *and* high linear flow rate (at least 1,500 cm/hr). As such the

claims are *not* anticipated by Lihme; that is, "the identical invention is not shown in as complete detail as is contained in the claims," nor are the elements "arranged as required by the claim." MPEP § 2131, citing *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1239, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989), and *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

For at least these reasons, Lihme does not anticipate the pending claims. Reconsideration and withdrawal of this rejection is requested, therefore.

B. Flickinger

Flickinger relates to an "an expanded bed process and system that includes an adsorbent material that is exceedingly mechanically stable at temperatures *in excess of 40° C.*; base-stable" and including an adsorbent material that "possesses a significantly high and surprisingly substantially consistent dynamic protein binding capacity when expanded at high fluid velocity (i.e., *greater than about 100 cm/hour*)." (Flickinger at col. 5, lines 47-58, emphasis added). The expanded bed adsorbent material disclosed in Flickinger "includes particles having a zirconium oxide core, the surface of which is modified for protein separation applications with a surface-modifying material" (col. 6, lines 66-67 through col. 7, lines 1-2). Yet, Flickinger does not disclose a fractionation method at high linear flow rate (at least 1500 cm/hr) *and* at high temperature (at least 50°C). Indeed, it is highly likely that a column run under the high flow rates prescribed in the claims would be non-functional (*i.e.*, not enabled).

With respect to linear flow rate, Flickinger provides a large prophetic range. For example Flickinger states that "[u]sing the surface modified zirconium oxide spherules, stable beds of classified particles over a range of linear fluid velocities at least about 100 cm/hour, and as high as 4000 cm/hour, can be attained" (col. 8, lines 54-57). In the Experimental Examples, Flickinger demonstrates actual linear flow rates of 100-220 cm/hr (*see e.g.,* col. 25, lines 37-39). In one experiment, the effect of "fluidization velocity" (linear flow rate) for columns comprising slightly different preparations of adsorbent particles was evaluated. Table V shows that the flow rates tested for one column were 109 cm/hr, 164 cm/hr and 215 cm/hr. Flow rates tested for the second column were 109 cm/hr, 110 cm/hr, 158 cm/hr, 200 cm/hr and 220 cm/hr. (See Flickinger, col. 27, Table

V). However, no correlation can be made between the dynamic binding capacity ("DBC") and the flow rate. Indeed, results indicate that when the first column had the same DBC when run at 109 cm/hr or at 215 cm/hr (a doubling of flow rate). Results are similarly negligible for the remaining samples. For example, the second column shows the same or worse DBC when run at 110 cm/hr or 220 cm/hr. (Flickinger, col., 27, Table 5).

Dynamic binding capacity is strongly dependent on the flow rate (and typically drops significantly above a certain critical flow rate, which will be dependent on the protein, adsorbent and raw material applied). Notably, Flickinger fails to provide any experimental data for flow rates over 200cm/hr, so the extremely high flow rates prophetically presented in Flickinger and recited in the present claims are unknown areas of experimentation in Flickinger.

Figure 4 of Flickinger discloses the relationship between linear flow rate and bed expansion. Bed expansion is the simple ratio (H/H0) between the bed height at zero flow (H0) and the bed height at a given flow (H). For expanded bed chromatography to function, a small amount of bed expansion is required (e.g. H/H0 = 1.2). However, there is also an upper limit, at which the flow rate becomes too high, making the bed unstable as the particles in the bed no longer sink down under gravity, but are physically carried away by the liquid flow. Above this upper limit of bed expansion, the column breaks down as particles are carried away. The skilled artisan knows that the practical upper limit for bed expansion lies around 3.5 above which the interface between the bed and the liquid head space becomes highly undefined and a significant amount of beads/particles may begin to leave the column with the upward flow. As Flickinger is already operating close to the upper limit at a linear flow rate of 200cm/hr, there is clear incentive *not to increase* the linear flow rate further. If this were done, the column bed would destabilize and the column would be non-functional. Thus, the skilled artisan would reasonably conclude that Flickinger *does not* provide an enabling disclosure for flow rates above about 200 cm/hr.

With respect to temperature, Flickinger indicates that the feedstock can be hypothetically be loaded through the expanded bed at temperatures "greater than about 30°C, preferably greater than about 50°C, which is particularly advantageous for very viscous feedstocks that flow at elevated temperatures." (Flickinger at col. 3, lines 32-36). In the Experimental Examples, it appears that a

majority of the studies were carried out with the feedstock at a temperature of 4°C or room temperature. Thus, Flickinger explains that "BSA solutions were either made fresh at the start of each experiment or were stored at 4°C for at most several days prior to use." (Flickinger at col. 20, lines 54-55). One experiment did explore protein adsorption at elevated temperatures, however. (*Id.* at col. 27, lines 62-67 to col. 28, lines 19-25). In this experiment, a "hot water circulation jacket system" was used around the column, while "[i]nlet fluids were preheated to the indicated temperature." (Flickinger at col. 27, lines 65-76). The three different temperatures were 25°C, 40°C and 44.5°C. (*See* Figure 11). No tests were performed at or above 50°C.

Like Lihme, Flickinger thus provides no examples, prophetic or otherwise, in which a temperature of at least 50°C is used *and* in which the linear flow rate is at least 1500cm/hr. As discussed above, flow rates much above 200 cm/hr would likely be non-functional in conjunction with Flickinger's columns and bed materials. Accordingly, the claims are *not* anticipated by Flickinger as "the identical invention is not shown in as complete detail as is contained in the claims," nor are the elements "arranged as required by the claim." (MPEP § 2131; citations omitted).

For at least these reasons, Flickinger does not anticipate the pending claims, and reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) is respectfully requested.

VI. Claim rejection – 35 U.S.C. § 103(a)

Claim 5 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,837,826 to Flickinger ("Flickinger") as evidenced by Protein Marker Broad Range in view of WO 02/096215 to Lihme ("Lihme") and/or Olander *et al.*, *Scandinavian Dairy Information*, 2001 (2): 22-25, ("Olander"). Applicants respectfully traverse this ground for rejection. As described above in section V, neither Lihme nor Flickinger anticipate the pending claims. Moreover, no permutation of teachings reasonably gleaned from these references could had led the skilled artisan to consider chromatographic conditions including both a high flow rate *and* a high temperature. In fact, both Lihme and Flickinger *teach away* from high flow rates, as recited in the claims, and Lihme teaches that the effect of temperature on chromatographic fraction is unpredictable. Neither Protein Marker Broad Range nor Olander cures these deficiencies.

A. Lihme teaches away from high linear flow rates

As described in section V, Lihme does not disclose a method of fractionation that includes both a high flow rate *and* a high temperature. In fact, Lihme *teaches away* from high linear flow rates (*e.g.*, a flow rate above 450 cm/hr). In the Experimental Examples, Lihme assesses various chromatographic parameters, and in Example 9, evaluates the effect of flow rate on sample yield. (Lihme at page 34). Lihme tested four different linear flow rates and recorded the yield of two different proteins (lactoferrin and lactoperoxidase) isolated from sweet whey. The four different flow rates tested were as follows: 7.5 cm/min (450 cm/hr); 10 cm/min (600 cm/hr); 15 cm/min (900 cm/hr); and 25 cm/min (1500 cm/hr). As shown in the second table at page 34 (and reproduced below), the trend is clear: the higher the flow rate, the lower the yield. In fact, the *lowest yield* for both proteins is obtained with the *highest flow rate*.

Column	Linear flow	Yield of LP per L whey loaded	Yield of LF per L whey loaded
A	7.5 cm/min (450 cm/hr)	29 mg	71 mg
B	10 cm/min (600 cm/hr)	29 mg	60 mg
C	15 cm/min (900 cm/hr)	27 mg	61 mg
D	25 cm/min (1500 cm/hr)	19 mg	55 mg

Yield dropped 35% for lactoperoxidase and 23% for lactoferrin when the flow rate was increased from 450 cm/hr to 1500 cm/hr. After a review of this data, there would be no reason for the skilled artisan to consider using a flow rate higher than 450 cm/hr for a related chromatography application; the skilled artisan would *expect* lower yields at higher flow rates.

B. Lihme teaches that the effects of temperature on chromatographic fractionation are unpredictable

Another chromatographic parameter explored by Lihme is the effect of temperature on protein fractionation from sweet whey (*see* Lihme Example 11, at pages 36-37). In the experiment,

Lihme isolated lactoperoxidase and lactoferrin from sweet whey under three different temperature conditions: 4°C, 22°C and 50°C. The data in Example 11 is inconclusive at best, and arguably *does not* support the use of higher temperatures. As shown in the second table at page 36 of Lihme (and reproduced below), an increase in temperature from 4°C to 22°C causes *a decrease* in yield of lactoperoxidase from 14 mg to 12 mg. Conversely, the same temperature shift causes an *increase* in yield of lactoferrin – the lactoferrin yield doubles, from 15 mg to 30 mg. However, the opposite result is obtained when the temperature is raised from 22°C to 50°C. That is, there is an increase in lactoperoxidase yield from 12 mg to 19 mg, while there is a fairly dramatic decrease in lactoferrin yield, from 30 mg down to 19 mg.

Column	Loading temperature	Yield of LP per L whey loaded	Yield of LF per L whey loaded
A	4°C	14 mg	15 mg
B	22°C	12 mg	30 mg
C	50°C	19 mg	19 mg

While the yield of lactoperoxidase is higher in the 50°C sample, the lower yield of lactoperoxidase at 22°C and the lower yield of lactoferrin at 50°C as compared to 22°C would leave the skilled artisan in doubt as to the accuracy of the data points and the value of increasing the temperature to 50°C. At best, the skilled artisan would conclude that temperature effects are unpredictable, and that for *some* whey proteins, a higher temperature may provide higher yields, although Lihme's data clearly indicate that the "higher temperature" would have to be determined empirically for each protein, and that 50°C is not an appropriate "low" starting point for optimizations (*i.e.* temperature of "at least 50°C"). Alternatively, and more likely, the skilled artisan would consider the data completely inconclusive and would revert to "conventional temperatures" in the range of 10°C.

More importantly, there is no reason the skilled artisan, after reading Lihme, would consider combining a high flow rate with a high temperature (*e.g.*, at least 50°C). Not only does Lihme teach away from linear flow rates "of at least 1500 cm/hour," Lihme clearly illustrates the unpredictability of temperature on overall yield. Thus, after having read Lihme, the skilled artisan would reasonably conclude that the yield from a hypothetical chromatography system using a linear flow rate of at least

1500 cm/hour with a sample fluid temperature of at least 50°C would be unpredictable at best, and as the data in Lihme strongly suggests, the yield would actually be poor or extremely poor.

C. Flickinger teaches away from high flow rates

As detailed above in section V, Flickinger also teaches away from high linear flow rates. As described in section V, the data shown in Figure 4 of Flickinger indicates that the Flickinger chromatographic systems are already operating close to the upper limit at a linear flow rate of 200cm/hr (bed expansion value H/H0 of 3.5). With a slightly higher flow rate, bed destabilization will be an issue. Thus, there is clear incentive *not to increase* the linear flow rate further (*i.e.*, to prevent bed destabilization) in the methods taught by Flickinger. Thus, while Flickinger may mention flow rates higher than 200 cm/hr, in light of the data actually presented in Flickinger and in light of the teaching of Lihme, the skilled artisan would not reasonably consider such flow rates a realistic possibility or at all beneficial.

Indeed, Flickinger had the opportunity to increase the linear flow rate over 200cm/hr, but did not do so. If it was not obvious to Flickinger to do so, it would not be obvious to the skilled person reading Flickinger to do so – and particularly not obvious in view of the teachings of Lihme.

D. Flickinger's examples do not use samples as recited in the claims; therefore, Flickinger's results are not predictive of methods using such samples

It is noted that the Experimental Example in Flickinger used a "feedstock" comprising a solution of bovine serum albumin ("BSA") at a concentration of 4 mg/ml to assess the protein adsorption characteristics of the zirconium adsorbent beds. (*See e.g.,* Flickinger at col. 20, lines 19-20, 30-32 and 54-55). No actual samples (*e.g.*, milk, whey, etc.) were tested. It is well known that real raw materials (such as those listed in claim 1), having a high dry matter content and a high viscosity, have a complex compostion also comprising non-protein substances such as carbohydrates, polysacharides and lipids and even reactive species such as polyphenols as well as a high microbial bioburden, behave very differently with respect to adsorption kinetics for a specific protein. Accordingly, the results shown in Flickinger are not necessarily predictive of results using natual raw materials, such as those recited in the claims. For example, while Flickinger indicates that for the

BSA feedstock "elevating the loading temperature from 25° to approcimately 45°C … incresases [DBC] by one-third," such a result may not be obtained using natural raw materials. In fact, after having read Lihme, in which the effects of temperature were found to be *unpreditable* when isolating proteins from *sweet whey*, the skilled artisan would be doubt the merit of combining high temperatures with actual samples.

E. Protein Marker Broad Range and Olander do not cure the deficiencies of Lihme and Flickinger

The "Protein Marker Broad Range" is described as follows:

> Protein Marker, Broad Range is a mixture of purified proteins with known amino acid sequences. They are resolved to 13 sharp bands when analyzed by SDS-PAGE (Tris-Glycine) and stained with Coomassie Blue R-250 (1). Two bands (BSA, MW 66.4 kDa and Triosephosphate isomerase, MW 26.6 kDa) are at double intensity to serve as reference points.

(http://www.neb.com/nebecomm/products/productp7702.asp). This "reference" does not provide information regarding chromatography or fractionation methods, and certainly does not describe the effects of temperature or flow rate on chromatographic methodoligies.

Olander provdies a description of expanded bed adsorption technology, and broadly describes the isolation of proteins from a raw material such as whey. (*See e.g.*, Olander at page 22-25). Yet, Olander is silent with respect to temperature. Regarding flow rate, Olander describes a two-column system and a three-column system, both of which handle a 690,000 L whey stream in 24 hours (page 25). It appears that all of the columns have a diameter of 1.5 meters (*id.*). These are the same example systems provdied in Lehme; thus the flow rates for these two systems will be 814 cm/hr for the two-column system and 542.6 cm/hr for the three-column system. See ection II, above, for complete calculations. Both values are well below the claimed linear flow rate of "at least 1,500 cm/hr."

E. Summary

In summary, the skilled artisan would not "obviously" have derived the claimed methodology from the teachings of Lihme, Flickinger, Olander, and the cited protein makers. To the contrary, both Lihme and Flickinger emphatically *teach away* from high flow rates, and none of the references evidences that high temperatures would be beneficial in any way in the fractionation of samples as claimed. This obviousness rejection is improper, therefore, and its reconsideration and withdrawal is respectfully requested.

VII. Double patenting

Claims 1-7, 9-13 and 15-17 are rejected under the judicially created doctrine of non-statutory obviousness-type double patenting in light of claims 1, 3-5, 7-16, 19-23 and 27-33 of U.S. Patent Application No. 10/478,111 (issued as U.S. Patent No. 7,812,138) in view of WO 02/096215 to Lihme ("Lihme") and/or Olander *et al.*, *Scandinavian Dairy Information*, 2001, vol. 2, pp. 22-25 ("Olander"). Office Action at page 10.

Claims 1-7, 9-13 and 15-17 are also rejected under the judicially created doctrine of non-statutory obviousness-type double patenting in light of claims 1-23 and 26-28 of U.S. Patent No. 7,368,141; claims 18-31 of U.S. Patent No. 6,783,962; claims 1-15 of U.S. Patent No. 6,498,236; or claims 1-6 of U.S. Patent No. 6,620,326 in view of Lihme and/or Olander. (Office Action at page 11).

Applicants respectfully traverse these grounds for rejection. Both rejections are based on a misinterpretation of "a linear flow rate of at least 1,500 cm/hour." This misinterpretation and its correction are detailed above in section II, and so applicants will not repeat the same comments here.

Applicants submit that none of the claims cited by the examiner recites or conveys *both* "a linear flow rate of at least 1,500 cm/hour" *and* a "temperature of at least 50°C." Thus, the cited claims do not anticipate the pending claims, nor do they render the present claims obvious. Withdrawal is warranted, therefore, of these obviousness-type double patenting rejections.

CONCLUSION

Applicants submit that this application is in condition for allowance, and they request an early indication to this effect. Examiner Kim is invited to contact the undersigned directly, should he feel that any issue warrants further consideration.

In addition, the Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, then applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of relevant fee(s) from the deposit account.

Respectfully submitted,

Date December 9, 2010

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